

Diagnosis and Management of Gastroenteropathy Associated to Non-steroidal Anti-Inflammatory Drugs

Stella Ilone, Marcellus Simadibrata

*Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

** Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia/ Dr. Cipto Mangunkusumo General National Hospital, Jakarta

Corresponding author:

Marcellus Simadibrata. Division of Gastroenterology, Department of Internal Medicine, Dr. Cipto Mangunkusumo General National Hospital. Jl. Diponegoro No. 71 Jakarta Indonesia. Phone: +62-21-3153957; Facsimile: +62-21-3142454. Email: prof.marcellus.s@gmail.com

ABSTRACT

Non-steroidal anti-inflammatory drugs (NSAIDs) is a group of drugs used to treat pain, inflammation, and fever. High consumption of NSAIDs associated with high gastrointestinal side effects. Common complaint from patients, which ranging from mild heartburn to the onset of gastrointestinal bleeding, often complicates the adequate administration of NSAIDs. Various methods have been developed to reduce the likelihood of gastroenteropathy complication. Early diagnosis, appropriate prompt treatment, as well as adequate monitoring will reduce morbidity and mortality from complications due to NSAIDs. This paper will discuss the diagnosis and management of gastro-enteropathy NSAID through approaching the underlying pathophysiology.

Keywords: *non-steroidal anti-inflammatory drugs (NSAIDs), gastropathy, enteropathy*

ABSTRAK

Obat-obatan anti inflamasi non-steroid (OAINS) merupakan kelompok obat yang digunakan untuk mengatasi nyeri, inflamasi, dan demam. Seiring dengan tingginya tingkat konsumsi terhadap golongan obat ini, semakin tinggi pulalah efek samping gastrointestinal yang dilaporkan terkait dengan penggunaannya. Keluhan umum yang dirasakan pasien mulai dari nyeri ulu hati ringan hingga timbulnya perdarahan saluran cerna kerap menjadi penyulit dalam pemberian OAINS secara adekuat. Berbagai cara telah dikembangkan guna mengurangi kemungkinan terjadinya komplikasi gastro-enteropati. Penegakkan diagnosis secara dini, penanganan awal yang tepat, serta pemantauan yang adekuat akan menurunkan angka morbiditas dan mortalitas akibat komplikasi akibat OAINS. Pada makalah ini akan dibahas mengenai diagnosis dan tatalaksana gastro-enteropati OAINS melalui pendekatan patofisiologi yang mendasarinya.

Kata kunci: *obat-obatan anti inflamasi non-steroid (OAINS), gastropati, enteropati*

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) is a group of drugs used to treat pain, inflammation, and fever.^{1,2} High consumption of NSAIDs associated with high gastrointestinal side effects. Common complaint from patients, which ranging from mild heartburn

to gastrointestinal bleeding, often complicates the adequate administration of NSAIDs.³ Globally, incidence of NSAID-induced gastropathy is increasing along with the high consumption of NSAIDs. In the United States of America, approximately 70% of the population aged over 65 years is taking NSAIDs

once a week and as much as 34% consuming it every day. Based endoscopy data obtained in Indonesia, gastrointestinal complications due to NSAID ranging between 20-70%.³

These drugs are commonly used in patients with autoimmune or elderly patients with joint pain in order to suppress the inflammation process and pain. Furthermore, patients with cardiovascular disease often use NSAIDs wheter as single therapy or in combination with other anti platelet aggregation drugs to minimize the thrombus formation.² In these groups, gastrointestinal side effects become a problem which led to inappropriate drug discontinuation. Along with the progressing knowledge, efforts to prevent the gastrointestinal side effects associated with NSAIDs consumption is increasing. Prevention efforts began with the early diagnosis of patients who have high-risk to have gastrointestinal bleeding due to NSAIDs consumption to the administration of mucoprotective drugs and gastric acid-suppressive drugs.

Generally, the mechanism of action of NSAIDs is based on its ability to inhibit the biosynthesis of prostaglandins from arachidonic acid on the molecular level, by inhibit the cyclooxygenase (COX) which consists of two isoforms: COX-1 and COX-2. Both of these isoforms worked oppositely whereas COX-1 activation is protective in maintaining the integrity of the gastric mucosa and keeping the platelets in one piece, while COX-2 will increase along with the inflammation process which occurs. Inhibition to the gastroprotective prostaglandins will cause a variety of gastrointestinal side effects associated with the use of NSAIDs.^{1,4} These effects are dose dependent, and the use of slow acting NSAIDs which release slowly into the bloodstream, increasing the risk of gastrointestinal disruption.^{1,2} This paper will discuss the diagnosis and management of gastropathy and enteropathy due to NSAID as well as prevention which can be done to reduce the morbidity and mortality due to NSAIDs consumption.

EPIDEMIOLOGY

Gastro-enteropathy is a medical term used to describe abnormalities in gastric mucosa and the small intestine which characterized by subepithelial hemorrhage and/or mucosal damage or erosion. In particular, NSAID-induced gastro-enteropathy is a disorder of the gastric mucosa and intestine due to consumption of NSAIDs. The incidence of NSAID-induced gastropathy is relatively high due to widespread use.

In the United States of America, approximately

25% of patients with long-term use of NSAIDs will experience ulcers and about 2-4% will have bleeding or perforation in gastrointestinal tract. The incidence of gastrointestinal side effects have cause more than 100,000 hospitalizations per year and 7,000-10,000 deaths per year.² Gastrointestinal tract bleeding is the most often manifestation of bleeding which occurs as the result of antiplatelet use. Studies show the use of low-dose aspirin (75-325 mg) still increase risk of bleeding (OR = 2.07). The incidence rate of upper gastrointestinal bleeding due to NSAIDs reaches 1-2% per year and have mortality rate 5-10%, although the overall mortality rate is still low at 0.22% per year.² In Indonesia gastrointestinal bleeding due to NSAID gastropathy was ranked second after the rupture of esophageal varices. NSAID gastropathy itself was ranked second after gastropathy due to *Helicobacter pylori* infection.³ Classification of NSAID can be seen at Table 1.

Table 1. Classification of NSAIDs

Types	Chemical composition	Common NSAIDs
Salicylates	Derivatives of 2-hydroxybenzoic acid (salicylic acid)	Aspirin, diflunisal, and salsalate
Propionic acid derivatives or "profens"	Derivatives of arylacetic acids	Ibuprofen, dexibuprofen, ketoprofen, dexketoprofen, naproxen, fenoprofen, flurbiprofen, oxaprozin, and loxoprofen
Acetic acid derivatives	Derivatives of acetic acids	Indomethacin, diclofenac, nabumetone, tolmetin, sulindac, etodolac, and ketorolac
Enolic acid derivatives or fenamates	Derivatives of 4-hydroxy benzothiazine heterocycle	Piroxicam, isoxicam, meloxicam, tenoxicam, droxicam, and lornoxicam
Fenamic acid derivatives or fenamates	Derivatives of anthranilic acid	Mefenamic acid, flufenamic acid, tolfenamic acid, and meclofenamic acid
Phenylpyrazolones	Derivatives of 1-aryl-3,5-pyrazolidinedione	Phenylbutazone, oxyphenbutazone
COX-2 selective inhibitors	Diaryl-5-membered heterocycles	Celecoxib, rofecoxib, and valdecoxib
Anilides and sulphoanilides	Acetamides of aniline with or without a 4-hydroxy or 4-alkoxy group	Acetaminophen, phenacetin, and nimesulide

MECHANISM OF ACTION OF NSAIDS

Mechanism of gastric and proximal duodenal mucosal damage due to NSAIDs is already known, while the pathogenesis of small intestine damage due to NSAIDs is not known clearly. The occurrence of NSAID enteropathy involves more complex

mechanism than just excessive gastric acid secretion, it also involve intestinal bacteria and the NSAIDs enterohepatic recirculation.⁴ Several studies have found that the use of gastric acid suppressive drugs does not have satisfactory results in lowering the incidence of NSAID enteropathy.

NSAIDs consisting of carboxylic acid or enol groups which useful in the activation of COX inhibition. Prostaglandins which synthesized from arachidonic acid is an essential mediator of inflammation, pain, fever and became the main target of NSAIDs (Figure 1).

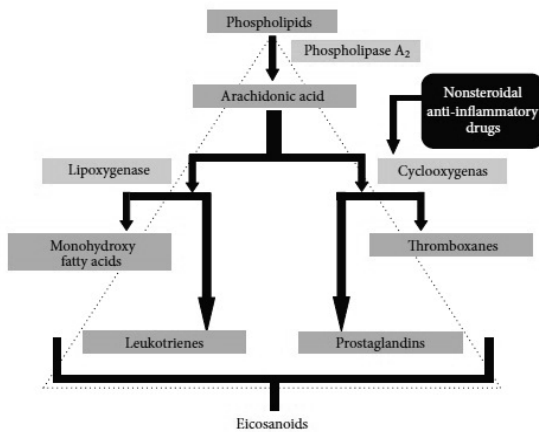


Figure 1. Mechanism of action of NSAIDs

The main pathophysiology of NSAID-induced gastrointestinal damage consists of three main mechanisms, which are inhibition of COX-1 and prostaglandins, changes in membrane permeability, and production of the main pathophysiology of NSAID-induced gastrointestinal damage consists of three main mechanisms, namely the inhibition of COX-1 and prostaglandins, changes in membrane permeability, and the production of pro-inflammatory mediators other pro-inflammatory mediators. Tissue prostaglandins are produced through two pathways: COX-1 and COX-2. COX-1 pathway is a constitutive pathway which dominant in gastroduodenal cytoprotection, renal perfusion and platelet activity. Otherwise, COX-2 pathway is pro-inflammatory pathway which manifests in the form of pain and fever. Inhibition of COX-1 pathway inhibits the production of prostaglandins which have an important role in gastric protection, especially in promoting mucosal blood flow, epithelial proliferation, as well as synthesis and secretion of mucus and bicarbonate. The inhibition of prostaglandin would disrupt protective factors mentioned above, which resulting in the gastric environment becomes more vulnerable to endogenous factors such as bile

salts, pepsin and acid.²

Suppression of mucosal prostaglandin will cause mucosal damage. This is related to the role of prostaglandins in improving many components of mucosal defenses such as bicarbonate and mucus secretion by epithelial cells which caused cell resistance to acid and pepsin as well as the promotion of epithelial damage repair.⁴ Prostaglandins produced mainly by gastroduodenal mucosal are PGE2 and PGI2. Both of these prostaglandins are potent vasodilator role in maintaining blood flow to the mucosa when the damage epithelial barrier in occurred. Increased blood flow have role in neutralizing the acid which diffuses back and in clean the toxic substances which enter into the sub epithelial.⁴

Based on this thought, now a new type of NSAIDs has developed with combination with NO or hydrogen sulfide, which both act as potent inhibitor of the leukocytes adhesion to the vascular endothelium, leading to damage of the gastric and intestine mucosal.

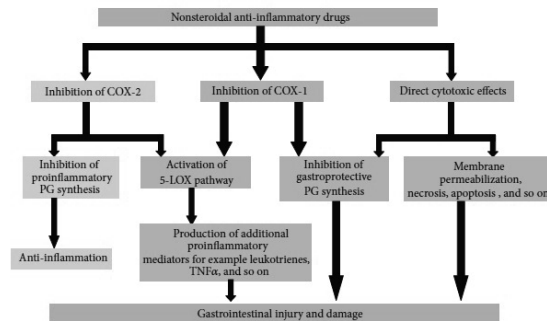


Figure 2. Pathophysiology of NSAID Gastro-enteropathy

Furthermore, NSAIDs, especially aspirin can directly damage the gastric mucosa and causes ulceration with its acidic properties. The influence of this acid give rise to the "ion trapping" phenomenon, which led to the accumulation of ionized NSAID, which then led to changes in permeability of the mucosa as well as induces apoptosis and necrosis of mucosal cells.² Inhibition of prostaglandin synthesis by NSAIDs causes stimulation of lipo-oxygenase pathway activation and increases leukotrienes production. Leukotrienes cause inflammation and tissue ischemia which led to injury in gastric mucosa. Moreover, activation of proinflammatory mediators such as TNF also occurs. This will increase the risk of microcirculation occlusion which will cause a decrease in gastric blood flow and release free radicals. Free radicals will bind with fatty acids which then cause lipid peroxidation and tissue damage.²

Pathogenesis of Gastroduodenal Damage

The ability of NSAIDs to cause damage to the gastrointestinal mucosa associated with its ability to inhibit the synthesis of prostaglandin. The use of NSAIDs that selectively inhibit COX-1 or COX-2 will reduce the risk of gastrointestinal disorders. The use of H₂-receptor antagonists and proton pump inhibitor (PPI) effectively shows that acid plays major role in the pathogenesis of gastroduodenal mucosal damage. In conditions where the mucosal damage has occurred, the acidic pH will penetrate the mucosa causing further damage and mucosal bleeding. This is due to the loss of the platelet aggregation ability at a pH of less than 4.⁴

Pathogenesis of Small Intestine Damage

Pathogenesis of small intestine is damage different than gastroduodenal damage. A longer time is needed in order to trigger the small intestine mucosal damage, compared to gastric mucosal damage. In general, the pathogenesis of small intestine mucosal damage similar to the pathogenesis of gastric mucosal damage. However, Reuter et al in 1997 showed that the suppressed synthesis of prostaglandins does not necessarily lead to ulcers formation and bleeding.

Important pattern which connected the use of NSAIDs with small intestinal mucosal damage is the absorption of secreted material in the ileum back into the duodenum through the enterohepatic circulation. (Figure 3).⁴ A mixture of bile components and NSAIDs can directly damage the intestinal mucosa through the uncoupling oxidative phosphorylation mechanism. Infiltration of neutrophils and the release of TNF- α are associated with mucosal damage, but increase in gram-negative bacteria is important in causing ulcers in patients with NSAIDs enteropathy.⁴

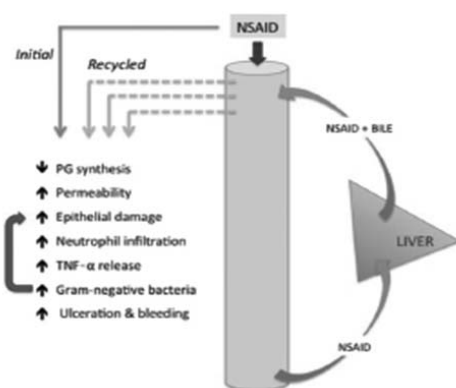


Figure 3. Pathogenesis of NSAID enteropathy⁴

RISK FACTORS OF NSAID GASTRO-ENTEROPATHY

Several studies have identified risk factors for NSAIDs gastrointestinal complications. Studies show patients with age over 65 years have a higher risk of gastrointestinal side effects than patients with age under 65 years (OR = 4.7), the use of a higher dose (OR = 8.0), the use of short-term NSAIDs (less than 1 month, OR = 7.2), the use of corticosteroids (OR = 4.4), and the use of anticoagulants (OR = 12.7).⁵

History of complicated or non-complicated ulcers is the most important risk factor for the occurrence of NSAID gastropathy. With a history of ulcers, the risk of gastrointestinal side effects increased 2.5-5 times. The risk become greater if complications occur in the history of previous ulcers.² Age is the second risk factor which plays role. Studies clearly showed an increased risk of NSAID gastropathy around the age of 60 years, even a significant increase for the age above 70 years. Age over 70 years have a similar risk with a history of previous ulcer.²

Some studies have found that short-term use of NSAIDs (less than 3 months) has higher risk of peptic ulcer. Although that risk will be reduced after a few months NSAID usage but it will not disappear in the long-term use. In a cohort study with 8000 rheumatoid arthritis patients showed that patients with cardiovascular disease have the highest risk of upper gastrointestinal complications with the usage of NSAIDs (OR = 1.84). Patients with previous history of peptic ulcer disease (OR = 2.29) and gastrointestinal bleeding (OR = 2.56) associated with increased risk.⁵

Another study showed that the risk of gastrointestinal complications is lower in the use of NSAIDs such as ibuprofen, naproxen, meloxicam, and etodolac and higher on NSAIDs such as sulindac, piroxicam, and ketorolac. It is suspected due to low doses in daily use for ibuprofen, while meloxicam and etodolac thought to have an effect on COX-2 more selectively. Increased risk of gastrointestinal complications in the use of sulindac, piroxicam, and ketorolac allegedly because longer half-life and therefore that longer mucosal exposure. A SOS study showed aceclofenac and ibuprofen have a low risk ($RR < 2$) for the occurrence of gastrointestinal side effects. Meloxicam, sulindac, diclofenac, and ketoprofen have intermediate risk ($RR = 2-4$), while tenoxicam, naproxen, piroxicam, and ketorolac high risk ($RR > 4$).⁵

The role of *H. pylori* infection as a risk factor of gastrointestinal bleeding in patients with NSAID therapy remains controversial. Most of the studies showed an increased risk of NSAID gastropathy

complications with *H. pylori* infection. One study showed an increased risk of 6.13 in the treatment of NSAIDs with *H. pylori* infection and it is higher compared to NSAID therapy alone (OR = 4.85). Another study indicated that presence of *H. pylori* infection with the use of NSAIDs increases the risk of gastrointestinal bleeding of 6.1 times.⁵

Eradication of *H. pylori* infection also showed a decreased risk of gastropathy OANS. But the role of *H. pylori* eradication in patients with NSAID therapy remains controversial. In a recent study, eradication of *H. pylori* may be as effective for lowering the risk of peptic ulcers either as primary or secondary prophylaxis at the beginning of NSAID use. But in the long-term use of NSAIDs, eradication did not show a significant benefit. This may be caused by the risk of NSAIDs gastrointestinal complications which is highest in the early months of use. In patients who did not experience the initial effects presumed to be able to tolerate these drugs without concerning their *H. pylori* status. Furthermore, some studies show that there is no significant difference in the use of low-dose aspirin. This is presumably because low-dose aspirin has a lower ulcerogenic effect than NSAIDs.⁵

The use of NSAIDs with gastrotoxic drugs also increase the risk of NSAID gastropathy. Antiplatelet use as mentioned above has a risk gastrointestinal complications. Antiplatelet without the use of NSAIDs have twice the risk and increase to 3.8-7.4 when used with NSAIDs. In patients with the use of antiplatelet, ibuprofen and naproxen are considered to have the most minimal cardiotoxic effects. However, the use of both still can affect the antiplatelet effects which can increase the cardiovascular risk.^{2,6}

The relationship between use of corticosteroids alone and risk of gastrointestinal bleeding is still unclear, but the use of corticosteroids increases the risk of bleeding when combined with NSAIDs.^{5,6} Treatment of NSAID gastropathy requires an assessment of the risk profile of each patient. Assessment of risk profile which used today is by the American College of Gastroenterology (2009).⁵

Table 2. Risk profile assesment by American College Gastroenterology

Risk	Risk profile assesment
High risk	History of previous complicated ulcers > 2 risk factors
Intermediate risk	age > 65 years old High dose NSAIDs use History of previous non-complicated ulcers
Low risk	Use with aspirin, corticosteroids, or anticoagulants No risk factor
Independent risk factor	<i>H. pylori</i> infection

DIAGNOSIS OF NSAID GASTRO-ENTEROPATHY

Diagnosis of the occurrence of NSAID gastro-enteropathy is based on the findings of patient history of complaints and signs which found by physical examination. The severity of mucosal erosions or ulcers that occur will determine the severity of the patient's clinical manifestations.

Forms of bleeding which can be encountered ranging from occult bleeding to life-threatening hematemesis melena. The occurred damage could be gastrointestinal bleeding, obstruction, and perforation.⁷ The most encountered clinical manifestation is vague gastrointestinal bleeding. Bleeding associated with inflammation usually ranges from 2-10 mL/day, whereas apparent bleeding found in 5-10% patients.⁸ A typical sign of NSAID gastropathy was the discovery of a circumferential shaped, fibrous, multiple, and thin stricture.⁹

Diagnosis via endoscopic examination of the upper gastrointestinal tract and radiographic examination using barium could be done to confirm diagnosis.⁷ Using the endoscopic examination, lesions can be viewed directly and followed by biopsy for additional examination. Furthermore, enteroscopy could also be done to see the small intestinal mucosal involvement. Pathological mucosal appearances could be edema, erosion, bleeding to stricture. Capsule endoscopy could also be done as one of non-invasive modalities.^{8,9}

PREVENTION AND THERAPHY OF NSAID GASTRO-ENTEROPATHY

Prevention

Prevention of NSAID gastro-enteropathy starts from identification of patients' risk group according to their risk factors. Moreover, thorough assessment of patients' condition are needed, especially of their indications and duration of NSAIDs administration. Several approaches are used in the prevention of NSAID gastropathy, such as combining with gastroprotector agents, replacing NSAIDs with COX-2 selective inhibitors, as well as *Helicobacter pylori* eradication.^{2,12} Substitution of ASA with clopidogrel in combination with PPI, especially omeprazole should administrated carefully because omeprazole can inhibit the action of cytochrome P450 which will inhibit clopidogrel metabolism into their active metabolites.^{2,3}

Prevention methods of mucosal damage and NSAID-induced peptic ulcer disease are by cotreatment

with PPI, H2 receptor antagonists, or misoprostol as well as substitution with COX-2 selective NSAIDs. Enteric coated NSAID administration give no significant results in reducing the incidence of peptic ulcer.

Acid Suppression Agents

Acid increases the risk of mucosal injury by NSAIDs and absorption of NSAIDs. H2 receptor antagonists and proton pump inhibitors (PPIs) are most commonly used suppression agents. PPI not only reduce acid but also maintain the gastric pH and has a role in the free radical binding.⁶

H2 receptor antagonists are the first drug used in preventing NSAID gastropathy particularly peptic ulcers. H2 receptor antagonists are currently available in four forms: cimetidine, ranitidine, famotidine, and nizatidine. H2 receptor antagonists work by directly inhibiting histamine H-2 by binding to its receptors in gastric parietal cells. Standard dose of H2 receptor antagonists which about twice a day use is considered effective in preventing the occurrence of duodenal ulceration, but protection against gastric ulceration is low. When administrated in high dose, H2-receptor antagonists may reduce the incidence of gastric and duodenal ulceration.

However, H2 receptor antagonists are also significantly less effective than the PPI in reducing the risk of ulcers. H2 receptor antagonists also did not show any significant results in case of gastric bleeding and prevention of ulcer complications. Currently, H2 receptor antagonists are not recommended for the prevention and treatment of NSAID gastropathy especially in asymptomatic cases.^{2,6}

PPIs are effective drugs in the acid suppression and prevent the incidence of peptic ulcers in patients with NSAID therapy. PPIs showed minimal side effect, therefore can be used in the long term. In two RCT studies, it was found that therapy with PPI (omeprazole) significantly decrease the incidence rate of ulcers associated with NSAIDs. Another study showed therapy with 15 mg or 30 mg lansoprazole per day is more effective than the use of misoprostol to prevent gastric ulcers in patients on NSAID therapy with negative *H. pylori*. In another RCT, it was found that PPIs may reduce the risk of NSAID gastropathy ulcer bleeding. In that study, it was found that risk reduction of gastrointestinal bleeding is 0.13 (95% CI = 0.09 to 0.19). However, PPIs are not effective for the treatment of mucosal injury in the distal part of the colon as well as NSAID colonopathy.^{2,5,6}

Prostaglandin Analogs

Prostaglandin analogs are used to replace prostaglandin formation which inhibited by NSAIDs. Prostaglandin in gastrointestinal mucosa works to increase mucosal bicarbonate secretion, stimulate mucosal blood flow and decrease mucosal cell turnover.⁵ Misoprostol is the most commonly used prostaglandin analog, was found able to decrease gastrointestinal ulceration induced by NSAIDs. Misoprostol is a E1 synthetic prostaglandin analog used to replace cytoprotector prostaglandin which decreased by NSAIDs. In the latest studies, combination of single-tablet diclofenac and misoprostol is effective for arthritis and decrease the incidence of NSAID gastropathy.

Studies have showed that misoprostol therapy of low-dose (400 mcg / day) has the same effectiveness as PPI in preventing duodenal ulcer. It was considered because of minimal incidence of *H. pylori* in the study. Another study showed there was no significant difference between PPI and misoprostol in preventing endoscopic ulcers. MUCOSA study showed that standard dose (4x200 mg) misoprostol is considered effective in preventing NSAID gastropathy ulcer (prevention of complications is up to 40%).¹² Misoprostol also have adverse effects on the gastrointestinal tract. The most frequent toxicities are diarrhea (10-30%) but it also can cause abdominal pain, nausea, and uterine bleeding. These limitations of misoprostol cause the patient compliance becomes vulnerable. Several studies showed that misoprostol is more inferior than PPIs in the treatment of gastric and duodenal ulcers associated with NSAIDs. Studies showed low doses of misoprostol have no significant side effects, but no more effective than standard dose of PPI. However, prostaglandin analogs fail to show a reduction in the risk of dyspepsia and other gastrointestinal side effects.^{2,5,6}

Rebamipide

Rebamipide is gastro-enteroprotective drug which working mechanisms are to stimulating endogenous prostaglandin formation, eliminating free radicals and reducing pro-inflammatory cytokines in the gastrointestinal tract. Several studies showed that rebamipide effectively prevents NSAID-induced gastropathy including aspirin. STORM Study showed that rebamipide as effective as misoprostol in preventing NSAID gastropathy with a better safety profile. Rebamipide also plays a role in the prevention of lesions in the small intestine mucosa. Rebamipide's metabolism on 3A4 substrate causes the

drug has advantages compared to PPIs' interaction with clopidogrel. In the case of gastric ulcers, rebamipide combination with PPIs proved to increase the cure rate and reduce the recurrence rate.³

Mucoprotector Agents

Sucralfate is aluminum salts based mucoprotector which form complexes adherent to duodenal ulcer. Sucralfate has a beneficial effect in the treatment of duodenal ulcer which only effective if NSAIDs therapy is stopped. Sucralfate is not effective in the prevention of gastric ulcers associated with NSAIDs.⁵

COX-2 Selective Inhibitors

Research on low gastrototoxic NSAIDs led to the development of COX-2 inhibitors. It was known NSAIDs inhibit COX leading to decreased production of prostaglandins. COX consists of two isoenzymes, namely COX-1 and COX-2. This encourages the discovery of COX-2 inhibitors. This class of drugs has anti-inflammatory properties similar to NSAIDs but has no gastrointestinal effects.

Examples of this class of drugs are rofecoxib and celecoxib. A RCT study of 742 patients over 50 years with arthritis compared two doses of rofecoxib (25 or 50mg) and ibuprofen (2400 mg) and placebo. In the study after 24 weeks, rate of ulcer was 9.6% for rofecoxib 25 mg, 14.7% for rofecoxib 50 mg, 45.8% for ibuprofen 2400 mg, and 9.9% for placebo. In another study which comparing celecoxib 200 mg to 500 mg naproxen, it was found the incidence of peptic ulcer was 9% for celecoxib and 41% for naproxen. Cochrane study showed the use of COX-2 selective inhibitors have lower gastroduodenal ulcer incidence (RR = 0.26) and complications from ulcers (0.39) compared to non-selective NSAIDs.^{6,10}

The combination of COX-2 inhibitors and low-dose aspirin has a smaller risk of bleeding compared with combination of NSAID and low-dose aspirin (RR = 0.72; 95% CI: 0.62-0.95). Moreover the combination of COX-2 inhibitor and anticoagulant also has lower risk of bleeding than conventional NSAIDs. The latest recommendation shows that COX-2 inhibitor is required as NSAIDs therapy in patients on therapy antikoagulan.^{6,11}

A study compared celecoxib 200 mg in combination with diclofenac 75 mg and 20 mg omeprazole for 6 months found that the incidents of peptic ulcers were 19% for celecoxib and to 26% for diclofenac/omeprazole and the incidents of gastrointestinal bleeding were 4.9% for celecoxib and 6.4% for diclofenac omeprazole. CLASS

study showed that celecoxib administration have less incidence compared to conventional NSAIDs within the first 6 months, but it failed to show a significant difference after one year use.^{2,5,6}

Although COX-2 inhibitor proved to reduce gastrointestinal toxicity but it has a correlation with the risk of cardiovascular events such as myocardial infarction and thrombosis. Beside that, the use of COX-2 selective inhibitors in combination with low-dose aspirin showed unsatisfactory results.

COX/5-LOX Inhibitors

Inhibition of COX also causes stimulation of the production of leukotrienes. Leukotriene is a potent inflammatory mediator. Because of this, development of a class of drugs which inhibit COX and leukotriene is begun, such as Licofelone and Benoxaprofen. In preclinical testing, Licofelone showed promising pharmacodynamic effect. Licofelone expected to have potent anti-inflammatory and analgesic effects but have minimal gastrointestinal effects. While development of Benoxaprofen has discontinued because its severe toxic effects, especially for liver.²

Lactoferrin

Some studies found that human recombinant lactoferrin can reduce gastric ulceration and gastrointestinal bleeding associated with NSAIDs therapy. The latest report also shows the C-lobe of lactoferrin are able to bind to the drug that binds to COX-2 and have the effect of preventing inflammation and bleeding of the stomach. In animal studies, it was obtained that the effectiveness of lactoferrin is same as COX-2.²

New Type NSAIDs

New types of NSAIDs have been developed such as NO-NSAIDs and H₂S-NSAIDs. Nitric oxide (NO) and hydrogen sulfide (H₂S) are potent vasodilators and they stimulate mucosal integrity. The interaction of NSAIDs with NO or H₂S are able to minimize side effects due to the inhibition of prostaglandin production.^{2,6}

THERAPY

Generally, treatments of NSAID gastro-enteropathy are by discontinuing NSAID or replacing it with an alternative therapy, PPIs administration, and lowering doses of NSAIDs. However, in serious cases such as ulcers and bleeding, the use of NSAIDs should be

Table 2. Recommendation of NSAID gastro-enteropathy prevention²

	Gastrointestinal Risk		
	Low	Mild	High
Low cardiovascular risk	Conventional NSAID	Conventional NSAID + PPI/misoprostol	Alternative therapy or COX-2 inhibitor + PPI/misoprostol
High cardiovascular risk (consider aspirin)	Conventional NSAID + PPI/misoprostol or alternative therapy	Conventional NSAID + PPI/misoprostol or alternative therapy	Alternative therapy Avoid NSAID or COX-2 inhibitor

*Low cardiovascular risk: No need of low dose aspirin or clopidogrel; High cardiovascular risk: Need of low dose aspirin or clopidogrel

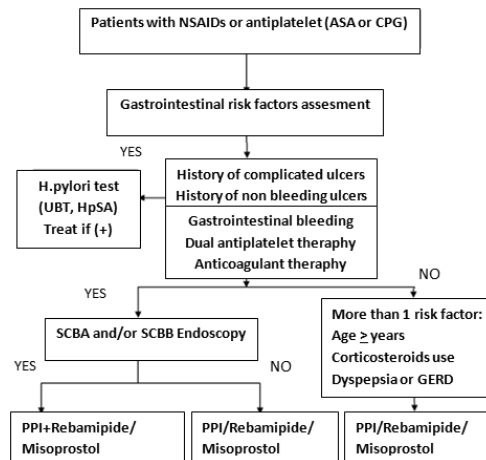
stopped. In severe cases, the treatment is divided into short-term and long-term therapy.⁶

Short-term therapy of peptic ulcers and gastrointestinal bleeding due to NSAID gastropathy are no different from therapy for other causes which including initial resuscitation, pharmacotherapy and endoscopic treatment. In long-term therapy, alternative therapy for NSAIDs should be given. In patients who requiring NSAID therapy, combination therapy should be given. H2 receptor antagonists may help heal ulcers in patients with NSAID therapy, but the rate of healing decreased significantly when patients keep taking NSAIDs. However, PPIs showed different results, PPIs are more effective than H2-receptor antagonists and misoprostol in healing ulcers in patients who continuing NSAIDs therapy. Furthermore, the combined use of PPIs and NSAIDs themselves also have the same risk of recurrent bleeding by administration of COX-2 inhibitor. However, combination of COX-2 and PPI has lower risk than the single administration of COX-2 (0 vs. 8.9). Therefore, the combination of a PPI and a COX-2 is the first-line therapy to reduce the risk of recurrent bleeding. This also applies to NSAID gastropathy with *H. pylori* patients.⁶ Prevention scheme in the treatment of NSAID gastropathy can be seen in Figure 4.³

CONCLUSION

The use of NSAIDs is increasing nowadays, which lead to high incidence of complications associated with patient gastrointestinal complaints. Complications can be mild or severe. Early diagnosis for assessing the severity of mucosal damage which occurs is based on patients' complaints and signs. Upper gastrointestinal endoscopy is still the gold standard in to assess mucosal damage which occurs.

The frequent NSAID-induced gastrointestinal side effects complicate the administration of the drugs according the appropriate dose and indication. Assessment of the patients' risk as well as the administration of various prevention methods are needed to be done in order to decrease the morbidity and mortality of gastrointestinal complications due to NSAIDs.

**Figure 4. Scheme of NSAID gastro-enteropathy treatment³**

REFERENCES

- Wallace JL. Mechanisms, prevention and clinical implications of non-steroidal anti-inflammatory drug-enteropathy. *World J Gastroenterol* 2013;12:1861-76.
- Mau Sinha LG, Prakash Kumar Shukla, Punit Kaur, Sujata Sharma. Current Perspectives in NSAID-Induced Gastropathy. *Mediators of Inflammation* 2013;11:2-12.
- Perkumpulan Gastroenterologi Indonesia. Konsensus nasional penatalaksanaan gastro-enteropati OAINS di Indonesia 2011.
- Wallace JL. NSAID gastropathy and enteropathy: distinct pathogenesis likely necessitates distinct prevention strategies. *Br J Pharmacol* 2012;165:67-74.
- Lanza FL, Quigley EM. Guidelines for prevention of NSAID-related ulcer complications. *Am J Gastroenterol* 2009;104:10.
- Gargallo CJ SC, Lanas A. Prevention and treatment of NSAID gastropathy. *Curr Treat Options Gastroenterol* 2014;12:15.
- Schellack N. An overview of gastropathy induced by non-steroidal anti-inflammatory drugs. *S Afr Pharm J* 2012;79:12-8.
- Berardi RR, Fugit RV. Peptic ulcer disease. In: DiPiro JT, Talbert RL, Yee GC, eds. *Pharmacotherapy: a pathophysiologic approach*. 8th ed. New York: The McGraw-Hill Companies 2011.
- Goldstein JL, Cryer B. Gastrointestinal injury associated with NSAID use: a case study and review of risk factors and preventative strategies. *Drug, Healthcare and Patient Safety* 2015;7:31-41.
- Tachei I, Kopacova M, Rejchrt S, Bures J. Non-steroidal anti-inflammatory drug induced injury to small intestine. *Acta Medica* 2010;53:3-11.
- Park SC, Chun HJ, Kang CD, Sul D. Prevention and management of non-steroidal anti-inflammatory drugs induced small intestinal injury. *World J Gastroenterol* 2011;17:4647-53.
- Becker JC, Domschke W, Pohle T. Current approaches to prevent NSAID-induced gastropathy – COX selectivity and beyond. *Br J Clin Pharmacol* 2004;58:587-600.